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Publication date:
2016

Document Version
Peer reviewed version

Foot-and-mouth disease virus capsid proteins; analysis of protein processing, assembly and utility as vaccines.

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Foot-and-mouth disease (FMD) remains one of the most economically important infectious diseases of production animals globally. The infection is caused by foot-and-mouth disease virus (FMDV), a member of the picornavirus family. The positive sense RNA genome of the virus includes a single, large, open reading frame that encodes a polyprotein. The intact polyprotein is never observed as it is processed, both during and after translation, to 15 different mature proteins plus a variety of precursors. The FMDV capsid protein precursor, P1-2A, is cleaved by the virus encoded 3C protease ($3C^{pro}$) to generate VP0, VP3, VP1 and the peptide 2A. Sixty copies of each of the capsid proteins "self-assemble" into empty capsid particles or with the RNA genome into infectious viruses. These particles normally lack 2A but it is possible to construct and isolate mutant FMDVs in which the cleavage of the VP1/2A junction is greatly inhibited, leading to the production of "self-tagged" virus particles that retain the 2A peptide. Interestingly, such mutant viruses acquire "second site" changes elsewhere within VP1.

Recent studies have shown that reducing the expression level of the $3C^{pro}$ relative to the P1-2A capsid precursor enhances the yield of processed capsid proteins and their assembly into empty capsid particles within mammalian cells. Such particles can potentially form the basis of a vaccine but they may only have the same properties as the current inactivated vaccines. We have expressed the FMDV P1-2A alone or with FMDV $3C^{pro}$ using a "single cycle" alphavirus vector based on Semliki Forest virus (SFV). Cattle vaccinated with these rSFV-FMDV vectors alone, produced anti-FMDV antibodies but the immune response was insufficient to give protection against FMDV challenge. However, vaccination with these vectors primed a much stronger immune response against FMDV post-challenge. In subsequent experiments, cattle were sequentially vaccinated with a rSFV-FMDV followed by recombinant FMDV empty capsid particles, or *vice versa*, prior to challenge. Animals given a primary vaccination with the rSFV-FMDV vector and then boosted with FMDV empty capsids showed a strong anti-FMDV antibody response prior to challenge; they were protected against disease and no FMDV RNA was detected in their sera post-challenge. Initial inoculation with empty capsids followed by the rSFV-FMDV was much less effective at combating the FMDV challenge. This prime-boost system, using reagents that can be generated outside of high-containment facilities, offers significant advantages to achieve control of FMD by vaccination.